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REVIEW

Intercellular Communication during Plant Development

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Multicellular organisms depend on cell-to-cell communication to coordinate both development and environmental responses across diverse cell types. Intercellular signaling is particularly critical in plants because development is primarily postembryonic and continuous over a plant's life span. Additionally, development is impacted by restrictions imposed by a sessile lifestyle and limitations on relative cell positions. Many non-cell-autonomous signaling mechanisms are known to function in plant development, including those involving receptor kinases, small peptides, and mobile transcription factors. In this review, we focus on recent findings that highlight novel mechanisms in intercellular signaling during development. New details of small RNA movement, including microRNA movement, are discussed, as well as protein movement and distribution of reactive oxygen species (ROS) in ROS signaling. Finally, a novel temporal mechanism for lateral root positioning and the implications for intercellular signaling are considered.

INTRODUCTION

The successful evolution of multicellularity required solutions to the problem of how to organize groups of cells and coordinate their collective growth and development. A key innovation was intercellular communication. The two primary groups of multicellular eukaryotes, plants and animals, independently evolved multicellularity and various mechanisms for effective intercellular communication. Plants rely extensively on local communication at either the tissue or cellular level. This is likely due to key differences in the developmental strategies taken by plants compared with animals.

Much of plant development occurs postembryonically, and organs are formed continuously over the life of a plant. As immobile organisms, plants depend on their ability to coordinate growth and development with environmental conditions. This coordination requires the ability to communicate over both long and short distances. Cells that interact with the environment must perceive and transduce environmental cues to other cells and organs. This requires both diversity in perception and specificity in response because the response to a given external cue must be appropriate and timely. As a result, plants show an astonishing plasticity in the size and number of organs produced in individuals of the same species under different environmental conditions.

The importance and complexity of cell-to-cell communication is given even greater weight because plant cells are confined to their relative positions by rigid cell walls. In the absence of intervening cell divisions, a given plant cell will be permanently surrounded by the same neighboring cells. Perhaps surprisingly, plant cell identities are based largely on positional information, indicating that a cell's neighbors also help to define its identity. The critical nature of positional cues in specifying cell identity can be observed during embryo development (Friml et al., 2003; Haecker et al., 2004; Breuninger et al., 2008; Schlereth et al., 2010) and was elegantly established in the plant root (van den Berg et al., 1995, 1997). The *Arabidopsis thaliana* root is a highly organized structure and provides an excellent, tractable system to study intercellular signaling during organ development (Benfey and Scheres, 2000). At the root tip, there is a central set of infrequently dividing cells called the quiescent center (QC; Figure 1; Dolan et al., 1993). Surrounding the QC is a layer of initial (stem) cells, which divide asymmetrically to regenerate the initial cell and form a new daughter cell that will proliferate and then differentiate (Dolan et al., 1993). Laser ablation experiments revealed three key intercellular signaling pathways between the QC and initial cells, between initial cells, and among cells within a lineage and demonstrated the importance of positional cues in root pattern formation (van den Berg et al., 1995, 1997).

In this review, we discuss some of the established paradigms of intercellular signaling mechanisms during development and highlight recent findings that reveal novel intercellular signaling mechanisms. First, an enhanced understanding of the movement of small RNAs (Dunoyer et al., 2010a; Molnar et al., 2010) has been obtained; in particular, microRNAs have been demonstrated to move between cells (Carlsbecker et al., 2010). Second, two articles expose the increasing importance and complexity of reactive oxygen species (ROS) status as a developmental signal. One publication demonstrates intercellular movement of a membrane protein that modulates ROS status (Meng et al., 2010), and the second shows that a mobile transcription factor modulates the distribution of different ROS in the root (Tsukagoshi et al., 2010). Finally, a novel developmental mechanism for establishment of the lateral root prepattern is discussed (Moreno-Risueno et al., 2010), and putative signaling outputs are considered.

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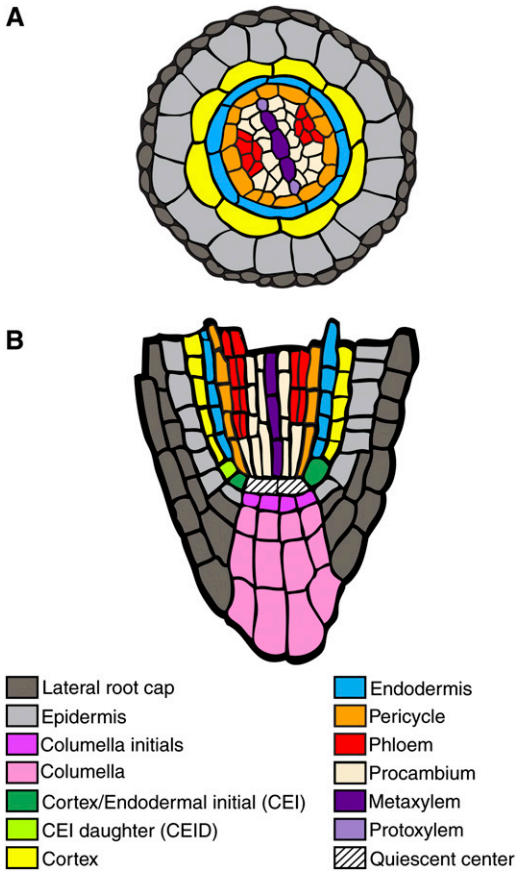

Figure 1. Schematic of Cell Types in the *Arabidopsis* Root Tip.

(A) Transverse section.
(B) Median longitudinal section.

Cell-to-Cell Communication during Plant Development: Which Lines Are Open?

Membrane Receptor Ligand–Mediated Intercellular Signaling

Signal transduction through plasma membrane receptors is an important way that plant cells communicate with their neighbors and interact with the environment. In *Arabidopsis*, there are over 600 putative receptor-like kinases (RLKs) and more than two-thirds of these are either transmembrane or membrane-associated kinases (Shiu and Bleecker, 2001, 2003). The incredible number of membrane RLKs implies that these proteins are important for the perception and transduction of a variety of signals from the cell periphery. Despite extensive efforts, a relatively small number of RLKs have been functionally characterized. Of these, only a subset has been experimentally linked to extracellular ligands. Ligands that are known to interact with RLKs are diverse and include peptides, metabolites, and bacterial flagellin (Diévart and Clark, 2004).

One of the most studied RLK receptor/ligand signaling modules in development is involved in perception and signal transduction of the CLAVATA3 (CLV3) peptide. *CLV3* encodes a small mobile peptide that promotes differentiation of stem cells in the shoot apical meristem (SAM; Fletcher et al., 1999). Three receptor complexes at the plasma membrane perceive the CLV3 peptide (Trotochaud et al., 2000; Rojo et al., 2002; Müller et al., 2008; Guo et al., 2010; Kinoshita et al., 2010). Signal transduction through these complexes restricts expression of WUSCHEL, a homeodomain transcription factor that non-cell-autonomously promotes stem cell identity (Brand et al., 2000). Thus, the CLV3 signaling system functions to regulate the critical balance between cell division and differentiation at the shoot meristem. A similar pathway has been identified in the root meristem. A transmembrane receptor, ACR4, perceives the CLAVATA3/ENDOSPERM SURROUNDING REGION-related (CLE) 40 peptide, which contributes to differentiation of the columella stem cells (De Smet et al., 2008; Stahl et al., 2009). Both ACR4 and CLE40 are expressed in differentiating columella cells, and through modulation of *WUSCHEL-RELATED HOMEOBOX5* (*WOX5*) expression, they maintain the size of the root stem cell niche by controlling the number of columella initial cells (Figure 1). Although the similarities between these root and shoot signaling modules are striking, there is a key difference between them: In the SAM, signals from the stem cells modulate the size of the niche, whereas in the root apical meristem (RAM), the signal comes from differentiated cells. Despite structural differences between the RAM and the SAM, signaling through CLE/RLK modules is important for maintaining both stem cell identity and the balance between cell proliferation and differentiation.

Novel Peptide Signals

The CLEs are some of the most studied peptide signals; yet they are just a few of the >1000 genes in the *Arabidopsis* genome encoding putative secreted proteins (Lease and Walker, 2006). Moreover, a recent publication indicates that novel small peptide-encoding genes remain to be identified. Matsuzaki et al. (2010) describe novel peptides that are required for maintenance of the root stem cell niche. The authors find that mutation of a posttranslational modifying enzyme, TYROSYLPROTEIN SULFOTRANSFERASE, causes pleiotropic effects, including a reduction in the size of the RAM region and altered root cell expansion. Exogenous application of known peptides with the Tyr sulfate modification only partially rescued the root phenotype, indicating the involvement of additional factors. A genome-wide search for open reading frames predicted to encode proteins that would undergo a Tyr sulfate posttranslational modification identified nine new genes, designated root meristem growth factors (RGFs). Genetic analyses showed that RGFs are positive regulators of PLETHORA (PLT) at both the transcriptional and posttranscriptional levels (Matsuzaki et al., 2010). PLT proteins are present in a gradient in the root tip and are necessary for maintenance of the stem cell niche (Galinha et al., 2007). The plant hormone auxin is also necessary for stem cell maintenance and is upstream of PLT (Ding and Friml, 2010); however, auxin does not affect RGF expression. This suggests that auxin and RGFs have independent roles in the regulation of PLT. Investigation into how the RGF signaling peptides are perceived and transduced should reveal whether similarities exist between the RGF and CLV3/CLE signaling modules and may provide insight into the mechanism for integration of signaling cues from both auxin and RGFs in specifying the root stem cell niche.

Cell-to-Cell Communication via Moving Transcription Factors

Differences between mRNA expression patterns and protein localization of various transcription factors suggested that proteins once thought of as purely cell autonomous could function as intercellular signaling molecules during development. One classic example of this comes from characterization of SHORTROOT (SHR), a member of the plant-specific GRAS family of transcription factors. SHR is required for formation of the two ground tissue layers: the cortex and endodermis. *SHR* mRNA is restricted to the vasculature, whereas SHR protein is found in the vasculature and cells in the adjacent layer, including the QC, cortex endodermal initial, cortex endodermal initial daughter, and endodermal cells (Figure 1) (Helariutta et al., 2000; Nakajima et al., 2001). In this adjacent layer, SHR protein is specifically required for asymmetric division of the cortex endodermal initial daughter as well as endodermal specification (Nakajima et al., 2001; Sena et al., 2004; Cui et al., 2007). Movement of SHR protein outward from the vasculature into the adjacent cells is highly regulated and may require both cytoplasmic and nuclear localization prior to trafficking out of the vasculature (Gallagher et al., 2004; Gallagher and Benfey, 2009).

The movement of several other plant transcription factors has been observed, including CAPRICE in root hair development (Wada et al., 2002) and SHOOTMERISTEMLESS, KNOTTED-LIKE IN *ARABIDOPSIS THALIANA*1/BREVIPEDICLUS (Kim et al., 2003), and DEFICENS (Perbal et al., 1996) in shoot development. The list of moving transcription factors continues to grow with the recent addition of two small basic helix-loop-helix (bHLH) proteins. TARGET OF MONOPTEROS7 (TMO7) is a small bHLH protein required for root formation in the embryo (Schlereth et al., 2010). The root meristem is partially formed from a single founder cell in the embryo, the hypophysis, which is recruited from the extraembryonic suspensor (Dolan et al., 1993; Scheres et al., 1994). Specification of the hypophyseal cell occurs in response to signals from the adjacent embryonic cells (Hamann et al., 1999). *TMO7* mRNA is restricted to the embryo proper, while the TMO7 protein is found in both the embryo and the hypophysis, indicating protein movement (Schlereth et al., 2010). Another small bHLH, UPBEAT1 (UPB1) was localized outside of its mRNA expression domain in the postembryonic root (Tsukagoshi et al., 2010). *UPB1* is expressed primarily in the lateral root cap and vasculature, while the UPB1 protein is found in all cell types in the elongation zone. Movement of TMO7 and UPB1 may be size dependent, as they are both very small bHLH proteins (~100 amino acids).

Mobile transcription factors functioning as intercellular cues are a key part of plant development, and the list of mobile proteins was recently expanded to include a membrane-associated protein (see details below; Meng et al., 2010). The frequency and variety of proteins that display intercellular movement suggest that this is an important mechanism in plants to coordinate developmental events among different cell types.

Small RNA–Mediated Intercellular Signaling

Small RNAs were discovered in petunia (*Petunia hybrida*) only 20 years ago (Napoli et al., 1990). We now know that there are two main types of small RNAs: small interfering RNAs (siRNAs), which have several subtypes and can arise from exogenous or endogenous RNAs, and microRNAs (miRNAs), which are processed only from endogenous RNA stem loops. Viral-induced siRNAs were known to move systemically through the plant vasculature for many years and lead to posttranscriptional gene silencing (Voinnet and Baulcombe, 1997), but movement of the endogenous small RNA moieties was initially less certain. One class of siRNAs, transacting small interfering RNAs (tasiRNAs), was inferred to move in the process of adaxial/abaxial patterning of leaves (Chitwood et al., 2009). Additionally, small RNAs derived from inverted repeats in the *Arabidopsis* genome were recently shown to be mobile molecules, but the functional significance of this movement remains to be discovered (Dunoyer et al., 2010b). Direct evidence for miRNA movement was largely missing, so miRNAs were suggested to function largely cell autonomously (Dunoyer and Voinnet, 2009). Nevertheless, there was some circumstantial evidence in support of miRNA movement. Analysis of phloem sap revealed the presence of both siRNAs and miRNAs (Buhtz et al., 2010; Varkonyi-Gasic et al., 2010), and grafting experiments with a miRNA biogenesis mutant showed that miRNAs in the shoot could downregulate their targets in the root, suggesting that miRNAs could function non-cell-autonomously (Buhtz et al., 2010). However, whether miRNAs acted as intercellular signals remained unresolved.

miRNAs as Intercellular Signaling Molecules

A Gradient of miR165/166 Directs Vascular Differentiation in Roots

This key question in miRNA function was recently resolved when intercellular movement of miRNA165/166 was shown to be required for the specification of xylem cells in the *Arabidopsis* root (Carlsbecker et al., 2010). The authors found that SHR and miR165/166 move in opposite directions leading to specification of xylem cell types. As mentioned above, *SHR* mRNA is expressed in the stele, but the protein is found in the stele and endodermal cell nuclei (Helariutta et al., 2000; Nakajima et al., 2001). In the endodermis, SHR and one of its direct targets, SCARECROW (SCR), are necessary for endodermal specification, yet over half the genes regulated by both SHR and SCR show their highest expression in the stele (Levesque et al., 2006; Cui et al., 2007; Sozzani et al., 2010). In addition to their ground tissue phenotypes, both *shr* and *scr* mutants have ectopic mature metaxylem in place of immature protoxylem, indicating roles for these transcription factors in xylem development.

Carlsbecker et al. (2010) began by determining where SHR and SCR activity is essential for the control of xylem differentiation. They expressed a nonmobile version of SHR in the stele of *shr* mutants and found that the plants still lacked protoxylem. However, ground tissue-specific SHR expression in a *shr* mutant resulted in visible protoxylem. When SCR was expressed in the ground tissue without SHR, neither the endodermis nor protoxylem was specified. These data indicate that protoxylem formation requires that both SHR and SCR are present in the endodermis and that their function must be non-cell-autonomous (Figure 2A).

PHABULOSA (PHB), a class III homeodomain leucine zipper transcription factor, was shown to be downstream of SHR and SCR (Levesque et al., 2006; Carlsbecker et al., 2010), but no direct interaction was found. A new *PHB* mutant, *phb-7d*, was isolated with a mutation in the miR165/166 target sequence, which prevents repression by those miRNAs (Carlsbecker et al., 2010). Similar to *shr-2* mutants, *phb-7d* mutant plants formed ectopic metaxylem and lacked protoxylem. Chromatin immunoprecipitation and microarray results showed that *miR165a* and *miR166b* were major direct targets for transcriptional activation by SHR. Further analysis of the *phb-7d* mutant revealed normal SHR expression but elevated *PHB* transcript levels. In *phb-7d* mutants, *PHB* was expressed not only as expected in the internal vascular tissue but also was found in the outer vascular and ground tissues. This indicated that miR165/166-mediated degradation functions to confine *PHB* mRNA to the internal vascular tissue (Figure 2).

miR165/166 is expressed in the endodermis, but its *PHB* mRNA target is found in the vascular tissue, implying that the miRNAs move (Figures 2A and 2B). This was demonstrated using a miRNA:green fluorescent protein (GFP) sensor construct in both *shr-2* and wild-type roots. In wild-type roots, expression of the miR165/166:GFP sensor was lower in the endodermis and outer vascular cylinder, but in *shr-2* roots, sensor expression was fairly constant throughout the root. This suggests that miR165/166 is active in the endodermis and outer vascular cylinder. Finally, the proposed movement of the miRNA was confirmed using in situ hybridization with probes to miR165/166. Together, these results indicate that mir165/166 moves from the endodermis into the vascular cylinder to restrict *PHB* expression and regulate xylem differentiation (Figures 2B and 2C). This complex system is a compelling example of how movement of regulatory molecules into and out of the vascular tissue sets up the gene expression patterns necessary for normal development.

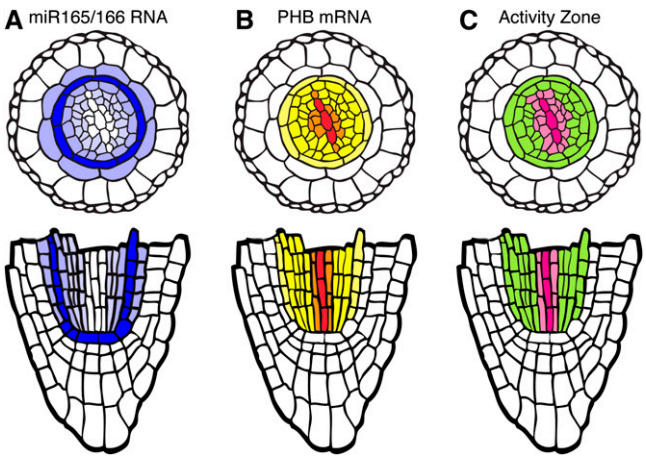

Figure 2. Schematic of the Expression of miR165/166 and PHB mRNA and Their Activity Zone.

(A) miR165/166 is expressed in the endodermis (dark blue) but moves outward to neighboring cell types (lighter blue).

(B) PHB mRNA is highly expressed in the metaxylem (red) and inner vascular cells (orange) and has lower expression in the outer vascular cells and endodermis (dark and lighter yellow, respectively).

(C) miR165/166 represses PHB mRNA in the activity zone (green), allowing PHB protein to specify metaxylem (dark pink). Note that PHB protein is found throughout the inner vascular cells (light pink) as well and presumably has other functions.

How Are These Small RNAs Transported: What Moves?

Despite clear evidence that small RNAs move, it is unclear which form of small RNA moves. Is it the long double-stranded RNA precursor, the short double-stranded siRNA, or the single-stranded mature siRNA? This question was addressed for 21-nucleotide moieties using both genetic methods and visualization techniques (Dunoyer et al., 2010a). Using a leaf chlorosis assay to measure the movement of a small RNA, the authors identified short RNA duplexes as the most likely candidates for movement. Using particle bombardment, the authors also visualized the movement of the trigger RNA fused to GFP or other fluorophores. Bombardment of single phloem cells resulted in movement to adjacent vascular cells, implying that siRNA duplexes could act over long distances.

The authors of a second article used grafting to show that many methylation-associated mobile small RNAs are 24 nucleotides long (Molnar et al., 2010). The authors used plants expressing both GFP and a GFP-derived hairpin, which should be processed to produce small RNAs, and monitored GFP expression. Using control shoots (scions) and mutant roots that were unable to produce 22- to 24-nucleotide small RNAs, grafting experiments showed that GFP was silenced in some roots. Sequencing of the small RNAs from the grafted mutant roots revealed 22- to 24-nucleotide small RNAs derived from the GFP hairpin. When the loci examined were known to be methylated, however, only 24-nucleotide small RNAs were trafficked to the root. Additionally, the authors demonstrated that the 24-nucleotide shoot-to-root mobile small RNAs could direct methylation at specified loci and are likely produced by RNA Polymerase IV, suggesting that movement may be necessary for the biological roles of 24-nucleotide molecules (Molnar et al., 2010).

tasiRNAs and miRNAs Differ in the Range of Movement: Unanswered Questions

Different small RNAs in plants vary in their biogenesis but not in their active forms. However, the range of movement seems to differ with siRNAs moving further than miRNAs. de Felippes et al. (2010) tested this by inserting the same small RNA sequence into several different tasiRNA or miRNA loci and then monitoring the movement of the resulting small RNAs. The small RNAs produced from miRNA loci were able to move 10 to 15 cells, but when the small RNA sequence was inserted in a tasiRNA locus, more small RNAs were produced and these spread much further. This indicates that the biogenesis of a small RNA has an effect on its mobility.

One of the remaining unanswered questions is how does the plant keep track of the loci where the small RNAs originate? One possible tracking mechanism may be spatial or temporal restriction of small RNA processing, where certain processing machinery proteins are only available at a certain time or place during development (de Felippes et al., 2010). Alternatively, the plant

could regulate movement of the mature small RNAs with their associated proteins, such as the ARGONAUTE proteins, which are necessary for the interaction with their targets (Voinnet and Baulcombe, 1997; Mi et al., 2008). It is reasonable to think that regulation could exist at both the processing and action steps, but the mechanisms of this control remain to be elucidated.

ROS Signaling and Intercellular Protein Movement

ROS are emerging as important modulators of developmental processes in diverse organisms. ROS are naturally produced as a by-product of metabolic processes; however, levels are tightly regulated as excess ROS can be cytotoxic. Plants also actively produce ROS through the activity of oxidases and peroxidases (Apel and Hirt, 2004). ROS participate in a variety of processes, including environmental response, growth, and development, such as root hair outgrowth and root gravitropism and elongation (Joo et al., 2001; Foreman et al., 2003; Liszkay et al., 2004). ROS-activated gene expression has been well documented in prokaryotes, fungi, animals, and plants, implicating redox-sensitive transcriptional regulators. In plants, a novel ROS-sensitive transcription factor, UPB1, was recently identified that modulates ROS status via direct regulation of peroxidase genes. UPB1 may also move from cell to cell to specify the position of cellular differentiation in the root (Tsukagoshi et al., 2010).

UPB1, a small bHLH domain–containing transcription factor, was identified based on its expression in the transition zone (TZ), a region of the root where cells transition from proliferation to differentiation. A UPB1 loss-of-function mutant had rapidly growing roots with a longer meristematic region, while plants constitutively expressing UPB1 had slower growing roots and shorter meristematic regions. Peroxidases were identified as direct targets of UPB1, implicating this protein in modulation of ROS status via transcriptional regulation of peroxidase genes. Peroxidases can increase or decrease ROS under different conditions, suggesting that the position of the TZ depends on ROS status. Using a variety of chemical, genetic, and histochemical approaches, Tsukagoshi et al. (2010) revealed the presence of two opposing ROS gradients that meet at the TZ. This suggests that ROS gradients determine the position where root cells begin to differentiate. The expression level of UPB1 is sensitive to levels of the ROS H_2O_2, suggesting that a feedback loop modulates ROS status.

As described above, *UPB1* mRNA is found predominantly in the lateral root cap (LRC), while the UPB1 protein is nuclear localized in all cell types in the elongation zone (Tsukagoshi et al., 2010). The LRC terminates as cells enter the TZ (Dolan et al., 1993), and removal of the root cap reduces mitotic activity in the root tip (Tsugeki and Fedoroff, 1999). These and other observations have led to a proposed relationship between the shootward edge of the LRC and progression to cell elongation and differentiation (Barlow, 2003). The putative movement of UPB1 from the LRC provides the first molecular support for this relationship. Thus, UPB1's function in demarcating the position where cells transition to differentiation appears to be twofold: first, by modulating ROS status, and, second, by potentially acting as a positional cue from the LRC into the internal cell layers.

In another investigation into the regulation of redox status in plants, a membrane-associated thioredoxin was found to move from cell to cell (Meng et al., 2010). Thioredoxins (TRXs) reduce disulfide bridges in oxidized proteins leading to either changes in the conformation (and activity) of a target protein or electron transport between the reductase and its target (Meyer et al., 1999, 2005). Thus, TRXs act as antioxidants through their response to ROS species and, in turn, are able to modulate the redox status of a cell. Meng et al. (2010) characterized TRX h9, which is required for multiple aspects of plant growth and development. *TRX h9* null alleles showed an overall reduction of seedling growth and a chlorotic dwarfed plant phenotype. The capacity for intercellular movement by TRX h9 is unusual, as no other characterized TRX proteins in plants or animals have been shown to undergo cell-to-cell movement. Additionally, intercellular movement of a membrane-associated protein is a novel mode of intercellular signaling. Whether other TRX proteins move, how TRX h9 moves, and how movement is linked to its function in regulating redox status are all unknown. However, the intercellular mobility of proteins that alter ROS status either through their transcriptional or biochemical activity suggests a new level of complexity in redox signaling in plants.

Biological Rhythms and Cell-to-Cell Communication

A biological rhythm can be defined as a self-sustaining change in a physiological process or behavior of an organism that occurs at regular intervals. Some of these rhythms are maintained by biological clocks, time-keeping mechanisms that maintain biological rhythms in the face of variable environmental conditions. Biological rhythms are observed over diverse time scales from hourly to annually and beyond. There are three main types of biological rhythms: circadian, infradian, and ultradian.

Circadian rhythms are the best characterized of biological rhythms, with a period of ~24 h. Most organisms coordinate their internal development and physiology with daylength and seasonal time using an endogenous mechanism known as the circadian clock (Song et al., 2010). Environmental cues, such as light and temperature, have inputs into the circadian clock and can entrain or adjust the clock's period. Circadian rhythms are temperature compensated, such that varying temperatures do not significantly alter the period (Bell-Pedersen et al., 2005). Readers interested in more details about circadian clock organization and function are directed to several recent reviews (McClung, 2008; Más and Yanovsky, 2009; Imaizumi, 2010).

Infradian rhthyms have a period of >24 h and can be tidal, lunar, seasonal, annual, or longer. These rhythms are often involved in reproduction; the reproductive cycles of many plants and animals display a circannual rhythm, occurring only once per year. By contrast, ultradian rhythms have periods of <1 d (seconds, minutes, or hours) and can be associated with either cellular or larger scale physiology. Examples of ultradian rhythms include the rhythm of the heart's pacemaker cells, which are responsible for the frequency of heart beats, the defecation cycle of *Caenorhabditis elegans* (45 s), and circumnutation during organ elongation in plants (Dekin and Haddad, 1990; Iwasaki et al., 1995; Shabala and Newman, 1997; Someya et al., 2006). The period of some ultradian rhythms is temperature compensated and remains constant at various growth temperatures (Liu and Thomas, 1994). Therefore, like circadian rhythms, ultradian rhythms may be regulated by an underlying biological clock.

Signaling and Biological Clocks

The circadian clock interacts with many signaling pathways, including those involved in stress and plant hormone signaling. The circadian clock's central oscillator is regulated by transcriptional and translational feedback loops (Locke et al., 2006; Zeilinger et al., 2006). Signaling between cells and tissues is an important mechanism to achieve synchrony in complex organisms (James et al., 2008). In the case of more rapid ultradian oscillations, signaling and other types of regulatory pathways may be used to control the central oscillator, and synchrony is likely to be required locally. In studies with unicellular eukaryotes, mutation of cellular signaling components caused arrhythmic phenotypes (Kippert and Hunt, 2000), suggesting that cellular signaling is a critical component of ultradian clock function.

The circadian requirement for an external input is less clear for ultradian clocks, where an environmental cue that synchronizes the clock is not evident (Kippert and Hunt, 2000). Nevertheless, similarities between circadian and ultradian clocks, such as their disruption by lithium, suggest that these clocks may share some regulatory mechanisms (Lloyd, 2006). Given the vastly different time scales, similarities in the regulatory mechanisms of biological clocks may indicate a commonality in the molecular mechanisms that keep time in living organisms. Although ultradian rhythms in plants have not received as much attention as circadian rhythms, a recent publication identifies an ultradian rhythm in gene expression that is linked to the periodic formation of lateral roots in *Arabidopsis* (Moreno-Risueno et al., 2010).

An Ultradian Clock Establishes the Prepattern for Lateral Root Development

One of the most intriguing features of lateral root (LR) development is the iterative nature of LR formation during growth. Despite environmental influence on its progression (Malamy, 2005), LR development generally shows a shootward distribution with the older LRs nearer the shoot and younger primordia nearer the root tip (Dubrovsky et al., 2006). Development of a LR primordium begins in the differentiated portion of the root with asymmetric division of certain pericycle cells (Malamy and Benfey, 1997). Prior to the asymmetric division, these cells, termed LR founder cells, exhibit expression from the synthetic auxin-responsive promoter DR5 (Dubrovsky et al., 2008). Whether LR founder cell specification occurs via reprogramming of differentiating pericycle cells or through a distinct developmental program involving certain competent pericycle cells remained an unresolved question.

The first evidence that developmental events leading up to LR initiation might occur prior to the presence of founder cells was the finding that DR5 reporter expression fluctuated in the protoxylem cells close to the root tip (De Smet et al., 2007; Moreno-Risueno et al., 2010). To examine DR5 expression in real time, Moreno-Risueno et al. (2010) fused the DR5 promoter to the luciferase gene, allowing characterization of the dynamic behavior of this marker. DR5 rhythmically pulsed with a period of ~6 h over a region of the root tip termed the oscillation zone (OZ), which encompassed the distal meristematic and the elongation zones (Figures 3A and 3B). The dynamic nature of DR5 expression in the OZ is consistent with the variable positioning of DR5:GUS expression in the protoxylem of individual roots.

DR5 expression is a marker for the transcriptional readout of auxin response/signaling but is also used as a proxy for auxin biosynthesis and localization/distribution. However, the inference that DR5 expression indicates auxin levels must be taken with caution as DR5 has been shown to be activated by other plant hormones (Nakamura et al., 2003). The oscillation of DR5 in the OZ could not be attributed solely to fluctuating auxin levels because other auxin-responsive promoters failed to show oscillatory expression (Moreno-Risueno et al., 2010). Additionally, OZ-localized exogenous auxin treatments did not replicate the outcome of the endogenous DR5 oscillation. These results do not support oscillation of auxin in the OZ; alternatively, the oscillation of DR5 was proposed to represent a broader oscillation in gene expression. Gene expression analyses revealed more than 2000 genes oscillating in phase with DR5 and another 1400 genes oscillating in antiphase with DR5. Transcriptional reporters for several candidate-oscillating genes exhibited oscillatory behavior with a similar period as DR5 (Moreno-Risueno et al., 2010).

Further characterization of the DR5:LUC expression revealed static points of expression following each oscillation. These sites were termed prebranch sites, as they turned out to reflect the positions at which LR development would subsequently occur. To address whether the periodic oscillations in gene expression and prebanch site formation could be described as a biological clock, the root's ability to compensate for changes in growth conditions was assayed. While changes in growth temperature altered root growth rate, no significant effect on prebranch site production was observed (Moreno-Risueno et al., 2010). Temperature compensation is a key feature ascribed to processes regulated by biological clocks; therefore, the oscillation leading to prebranch site production was termed the LR clock. Together, these results suggest an oscillatory genetic network is operating in the OZ to establish a temporal prepattern for LR development.

Periodic Formation of Structures in Plant and Animal Development

The regular formation of anatomical structures is a common developmental feature across diverse biological systems. During vertebrate embryogenesis, the segmentation pattern is established by the rhythmic production of vertebral precursors, the somites. With the same period as somite formation, a wave of gene expression sweeps through the elongating presomitic mesoderm (Pourquie, 2003; Dequeant and Pourquie, 2008). There are striking similarities to prebranch site formation in plant roots, where an oscillation in gene expression is linked to the periodic positioning of future LR sites. This similarity might reflect the convergent evolution of a developmental mechanism regulating periodic organ formation along a growing axis. Despite the broad similarity between the plant and animal clocks, there is a key difference in temperature compensation. In vertebrates, the size and number of somites is temperature compensated (Schröter et al., 2008), whereas in plants, the period of the LR clock is temperature compensated (Moreno-Risueno et al., 2010). This difference may be explained by developmental differences between plants and animals. In vertebrates, development is fixed

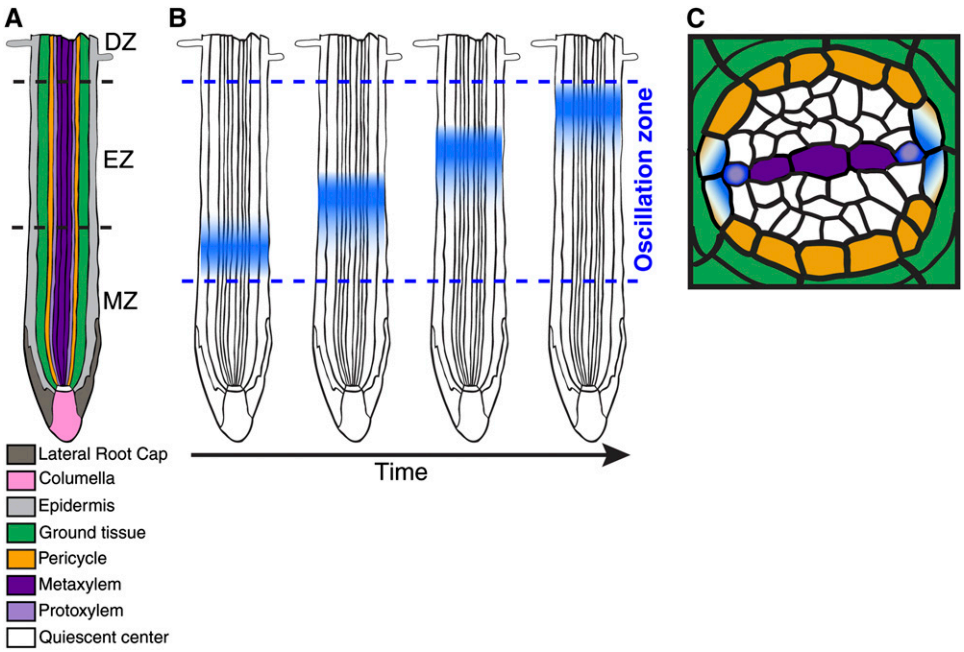

Figure 3. Wave of Gene Expression in the Oscillation Zone Establishes the Prepattern for LR Formation.

(A) Schematic of the *Arabidopsis* root tip, median longitudinal section in the xylem axis with each of the developmental zones: merstematic (MZ), elongation (EZ), and differentiation zones (DZ).

(B) Schematic of a wave of gene expression in the oscillation zone over time.

(C) The oscillation of DR5 is observed in the protoxylem; however, LRs develop from the pericycle. Thus, the outcome of the oscillation in the protoxylem (light purple with blue edge) may be signaled outward to the adjacent pericycle cells (blue-to-orange gradient).

and alterations in the number or size of vertebra could have serious adverse effects on fitness, while in plants, development is plastic with the number and size of organs being variable.

In the vertebrate segmentation clock, only cells at a certain position in the presomitic mesoderm are able to respond to the inductive clock signal. The position at which cells can be specified as competent to form the next somite is delimited by the crossing point of two opposing signaling gradients (Dubrulle and Pourquié, 2004). Given similarities in the periodic formation of structures and oscillation of gene expression in both the LR and segmentation clocks, could opposing signaling gradients in the root determine the position of prebranch site formation? Hypotheses regarding whether signaling gradients function in specifying prebranch site formation and the identity of these proposed gradients are key questions for future research.

Signaling Output and the LR Clock

Currently, the periodic formation of prebranch sites and bends in the root are the only known outputs of the LR clock; however, we can speculate that several signaling events may be required for LR clock function. At the cellular level, DR5 reporter expression shows fluctuations in the protoxylem cells in the OZ (De Smet et al., 2007; Moreno-Risueno et al., 2010). Because LR founder cell specification and initiation occur in the pericycle, this implies coordination between developmental events in the protoyxlem and the pericycle. Therefore, the outcome of the oscillation may be signaled to the adjacent pericycle layer (Figure 3C). Alternatively, it is possible that genes oscillating specifically in the pericycle lead directly to prebranch site formation.

The dynamic behavior of gene expression in the OZ suggests that the expression of oscillating genes behaves as a propagating wave over the longitudinal axis of the root (Figure 3B) (Moreno-Risueno et al., 2010). How this type of dynamic gene expression behavior is regulated remains an open question. One possibility is that intercellular signaling at the leading edge of the wave results in spatial amplification of the wave. The wave would dissipate if cells could not perceive the signal. Perhaps differentiated root cells fit this criterion, explaining why the waves of gene expression fail to propagate along the entire root length. Alternatively, it has been suggested that the oscillation in gene expression in the OZ may also be explained by an inhibitory signal from more mature cells to the adjacent OZ cells (Traas and Vernoux, 2010). However, propagation of gene expression waves toward the more mature cells is difficult to reconcile with this hypothesis. The role of signaling in both the output and control of the LR clock remains to be determined; however, observation of the oscillation at cellular resolution will likely be required to address this question.

CONCLUSION

Our understanding of how intercellular information is conveyed in plants frequently becomes outdated as plants reveal more

molecules that can act as mobile signals. Proteins once defined as cell autonomous, including transcription factors and membrane-associated proteins, as well as all types of small RNAs, exhibit intercellular movement. Additionally, novel mobile peptides continue to be identified, and the role of ROS as signaling molecules is becoming clearer as it seems that two opposing ROS gradients are important for root growth and development. These additional signaling molecules do not include the vast number of novel metabolites or peptides that are likely to be revealed as "omics" approaches become more sensitive. Additionally, as we begin to understand more about the dynamic events that underlie developmental processes, it is likely that the role of signaling in coordinating these events across cell types will become even more significant. It is clear that there is still much to learn, and as studies progress in diverse fields of plant biology, including growth, development, and environmental response, exciting new signaling networks will certainly be uncovered.

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